# TRANSLATOR CERTIFICATION

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I, Kerstin Roland, a translator fluent in the German language, on behalf of Morningside Evaluations and Consulting, do solemnly and sincerely declare that the following is, to the best of my knowledge and belief, a true and correct translation of the document(s) listed below in a form that best reflects the intention and meaning of the original text.

**MORNINGSIDE EVALUATIONS AND CONSULTING**

Kerstin Roland

Signature of Translator

Description of Documents Translated:
DE 41 10 087 A1: Pharmaceutical containing Benfotiamin and its use

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## Description

The invention relates to a pharmaceutical containing Benfotiamin and to its use.

Benfotiamin (S-benzoylthiamine-O-monophosphate) is a lipid-soluble form of vitamin B1. The symptoms of vitamin B1 deficiency are lack of appetite, vomiting, resorption disorders, fatigue, paralysis and mental changes such as loss of memory, confusion and depression. These deficiencies are known as Beri-Beri disease. Vitamin B1, a water-soluble vitamin, is therefore not a suitable pharmaceutical for treating these states of vitamin B1 deficiency because it has limited bioavailability (only about 5% of an oral administration is resorbed) and has retention properties. For this reason, vitamin B1 may have to be administered in very high doses.

It is already known to administer the lipid-soluble form of vitamin B1, namely Benfotiamin, in the form of coated tablets in order to achieve improved resorption in the intestinal tract compared to the water-soluble vitamin B1. Benfotiamin is cleaved upon absorption in the cell system and the active ingredient, namely thiamine, is released.

The disadvantage of the familiar application method is that a localized application is not possible due to the oral administration. Consequently, the dose to be administered must be so high that the site, from which for example a vitamin B1 deficiency is supposed to be eliminated or at which a therapeutically necessary concentration is supposed to be present, must contain sufficient Benfotiamin that it can be cleaved into the active ingredient thiamine (vitamin B1). If for example a painful inflammation of a foot joint caused by vitamin B1 deficiency is supposed to be treated, a sufficient quantity of Benfotiamin has to be administered to ensure that following the resorption in the intestinal tract enough Benfotiamin is present at the site to be treated, which is then cleaved into thiamine and available as the active ingredient. During this process, the organism of course transports the resorbed Benfotiamin not only to this site, but distributes it throughout the entire organism. As a result, the Benfotiamin is also cleaved in cells with no vitamin B1 deficiency, releasing thiamine, although this is not required in these cells. An increased vitamin B1 supply to the body expresses itself in an extremely unpleasant body odor.

It is the object of the present invention to overcome these disadvantages and create a pharmaceutical of the type mentioned above, which can be applied locally.

According to the invention, the object is achieved with a pharmaceutical, in which Benfotiamin is taken up and distributed throughout a carrier and which is applied topically to the skin.

If a carrier takes up Benfotiamin, the resulting ointment or cream can be applied for example locally to such areas of the skin, which cover the areas of the body that require treatment. The carrier ensures that the Benfotiamin stays in that location and offers the possibility of Benfotiamin penetrating through the skin into the cell system beneath. Dephosphorylation into S-benzoylthiamine (SBT) then occurs in the cell system as a result of phosphatases inherent to the cells. Thereafter, SBT is converted into thiamine by means of enzymatic debenzoylation, which



thiamine in turn is converted into cocarboxylase with metabolic activity.

It was found that the lack of sufficient quantities of cocarboxylase in diseased sites results in an accumulation of intermediary decomposition products such as pyruvate, lactate and ketoglutarate. This leads to inflammations, which are associated with pain. Following its penetration through the skin and conversion into cocarboxylase, Benfotiamin inhibits the accumulation of these toxic matters. Studies have shown that an antinociceptive effect is achieved, i.e. thiamine occupies pain receptors and consequently inhibits the transmission of the pain sensation.

Introducing Benfotiamin into the carrier opens up the possibility of applying Benfotiamin through targeted local action via the skin into the areas of the body requiring treatment, where it is then converted into the active ingredient thiamine and/or cocarboxylase. The advantages are not only that a localized application becomes possible, but also that due to the particular penetration mechanism and the subsequent release of thiamine a significantly more rapid administration of the active ingredient to the site to be treated is achieved. Additionally, it is possible to use considerably less Benfotiamin on an overall basis compared to the administration in the form of coated tablets, because only a relatively small portion of Benfotiamin is already converted into thiamine on the relatively short transportation path between the skin and the treated body areas before reaching the cell regions that in fact require treatment. The conversion mechanism of Benfotiamin into thiamine is carried out in the cells regardless of whether a disease pattern exists or not, i.e. in the case of oral administration such a conversion takes place directly following absorption in the cell system of the gastrointestinal tract. As a result, it must be ensured that the amount of Benfotiamin at the treatment site is still sufficient so that it can be converted on site into the active ingredients thiamine and/or cocarboxylase. These disadvantages are overcome with the topical external application, and also the effects of unpleasant body odor associated with a high dose of vitamin B1 are eliminated. The topical analgesic and antiphlogistic effects achieved with the external administration according to the invention can be achieved quickly, lastingly, within a targeted local area and, unlike oral administration, with significantly lower quantities of Benfotiamin.

In another embodiment of the invention, the carrier is a lipophilic carrier in ointment form.

This measure has the advantage that the pharmaceutical has the form of an ointment or a cream, which is easy to handle and can be applied with good adhesion on the human skin or be massaged into it. Benfotiamin can be distributed in the lipophilic carrier matrix for example as a finely dispersed solid matter. Massaging the ointment- or cream-like carrier into the skin shortens the penetration phase.

In a special embodiment of the invention, the carrier contains liposomes, in the aqueous interior of which the Benfotiamin can be found.

Liposomes are spherical shapes made of one or more concentrated lipid bilayers with aqueous interior. Vesicles like these can be produced by finely distributing – mechanically - the phospholipids (e.g. lecithin) in aqueous

media. The measure suggested here, namely to introduce the Benfotiamin in the aqueous phase in the inside of the liposomes, offers the considerable advantage that the Benfotiamin can be taken up in the lipophilic carrier relatively safely and protected from external influence. Furthermore this measures has the considerable advantage that the liposomes penetrate very quickly through the skin areas and release Benfotiamin only in the body's cells beneath the skin. This way, quick, targeted administration of the Benfotiamin into the areas of the body requiring treatment can be achieved. Upon release of Benfotiamin, the previously described conversion mechanism in the cells can take place and convert it into thiamine and cocarboxylase. This measure now offers the additional considerable advantage that Benfotiamin can be supplied to the body regions requiring treatment nearly completely, undecomposed, and encapsulated in the liposomes.

As a result, extremely rapid and targeted treatment is possible, using relatively small amounts of the active ingredient.

In another embodiment of the invention, the carrier is a lipophobic carrier containing detergents, which effect a distribution of Benfotiamin in the lipophobic phase.

This measure has the advantage that Benfotiamin can be taken up in a lipophobic carrier via detergents, which are known per se, so that the pharmaceutical approximately has the consistency of a fluid, which can be distributed very quickly and evenly if it needs to be applied across a large area. To this end, the lipophobic carriers can be such that they largely evaporate as soon as they are applied on the skin, forming a film-like layer on the skin. This is desirable, for example, when the skin areas are supposed to be covered by clothing immediately following the application of the pharmaceutical, without the clothing sticking to the treated skin areas and causing inconvenience.

In another embodiment of the invention, the pharmaceutical is applied in the form of an aerosol.

This measure has the advantage that the pharmaceutical can be applied quickly and easily on the skin. The Benfotiamin can be present as a suspension in a liquefied gas under pressure as the propellant and be applied to the body as the propellant is released as a finely dispersed solid matter. It is also conceivable to include Benfotiamin in a lipophilic or lipophobic phase in the propellant, so that the carrier along with Benfotiamin is applied onto the skin as a finely dispersed film-like coating after the aerosol comes in contact with the skin.

Studies have shown that a pharmaceutical of this type can be used to treat the following diseases: rheumatic disorders; general joint and muscle pain, irritated radicular syndrome of the spinal cord, cervical syndrome, shoulder-arm syndrome, symptoms resulting from polyarthritis, tennis elbow, stiff neck, lumbago, sciatic pain syndrome, intervertebral disk problems, arthrosis, polyneuropathy, neuritis, migraine, neuralgia, shingles and facial paralysis.

In all these applications, Benfotiamin, which is incorporated in ointment carriers, is applied to the appropriate skin area in the region of the diseases body parts and can unfold its effect very quickly and in a targeted manner, usually after just a few minutes.

The afore-mentioned characteristics and those explained below can of course be used not only in the described combination, but also in other combinations or alone, without departing from the idea of the present invention.

The invention will be explained more closely hereinafter with reference to a few select embodiments:

Example 1

5.0 g Benfotiamin is introduced in the familiar manner into 95.0 g unguentum emulsificans.

The resultant ointment is massaged into the skin, and a significant relief of pain was noticed following just a few minutes for the following disease patterns: rheumatic pain, general joint and muscle pain, irritated radicular syndrome of the spinal column, cervical syndrome, shoulder-arm syndrome, symptoms resulting from polyarthritis, tennis elbow, stiff neck, lumbago, sciatic pain syndrome, intervertebral disk problems, arthrosis, polyneuropathy, neuritis, migraine, neuralgia, shingles and facial paralysis.

Example 2

An aqueous saturated solution of Benfotiamin is prepared, wherein the aqueous phase is adjusted to a pH of 8 for better solubility.

Then the aqueous phase is mixed with lecithin, and while stirring vigorously and at the same time applying pressure surges on the liquid an emulsion is prepared, containing spherical structures measuring between 25 nm and 1 µm in diameter. The spherical liposomes enclose an aqueous phase, which contains the Benfotiamin. Depending on the quantity of lecithin that is added, a more ointment-like or a more cream-like emulsion is obtained.

The resultant emulsion is massaged into the appropriate areas of the skin, as described in Example 1, wherein the disease patterns were the same as those outlined in Example 1.

In all cases, consistently even faster effects were achieved.